PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Batra et al.	)	
	)	
Serial No.: 09/894,921	)	Examiner:
	)	Sharareh, Shahnam J.
Docket No.: 20243CA	)	
	)	Art Unit:
Filed: June 28, 2001	)	1617
	)	
For: "COMPRESSED TABLET FORMULATION"	)	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF CONRAD S. WINTERS UNDER 37 C.F.R. § 1.132

Sir:

I, Conrad S. Winters, hereby declare and say:

1. I am a citizen of the United Kingdom of Great Britain and I reside in Lansdale, PA 19446.

2. I graduated in 1993 from Bradford University located in Bradford, West Yorkshire, England with a Ph.D. in Pharmaceutical Technology.

3. I have been employed since 1993 by Merck & Co. I am currently located in West Point, Pennsylvania where I am Director of Formulation Development in the Department of Pharmaceutical Research. The focus of my work has been supervising the development of solid oral dosage forms, including design and definition of the formulation, process development and optimization and manufacture of materials to be used in the support of clinical trials in humans.

4. During my 12 years with Merck and Co. I have worked as a pharmaceutical formulator on many projects with specific responsibilities increasing over the years. I was a

member of the SINGULAIR® design team, I am a co-inventor on the once-a-day formulation patent for VIOXX®, and I had lead formulator responsibilities on ARCOXIA®.

5. I attach a copy of my resumè as Exhibit 1, which provides further information on my educational background and work experience and includes a list of my publications, patents and presentations.

6. I have read and understand the subject application, which includes claims directed to a compressed tablet comprising efavirenz, filler/disintegrant, superdisintegrant, binder, surfactant, filler/compression aid, lubricant, and solvent, wherein efavirenz is about 50% by weight of the total composition of the compressed tablet.

7. I have also read and understand the Office Action mailed May 23, 2005 concerning the subject application ("Office Action"), and I have read and understand US 6,238,695 ("Makooi"), Remington: The Science and Practice of Pharmacy, 19th edition, pp. 1616-1620 ("Remington"), and US 5,260,073 ("Phipps"), each of which is cited in the Office Action.

8. I comment and opine here on the Examiner's assertion in the Office Action that there is no distinction in the art between superdisintegrants and disintegrants.

9. The terms "disintegrant" and "superdisintegrant" are sometimes used interchangeably in reference to substances incorporated into a tablet to facilitate the tablet's breakup subsequent to administration. This circumstance is exemplified by Phipps which does not distinguish between disintegrants and superdisintegrants, but instead refers only to disintegrants. However, the failure in Phipps and other documents to make this distinction does not mean that none is recognized in the art.

10. It was recognized in the art at the time the subject application was filed (and is still so recognized today) that certain substances employed as tablet disintegrants are characterized as superdisintegrants based upon their superior performance and efficiency. Reference is made to Thibert et al., *J. Pharm. Sci.* 1996, 85: pp. 1255-1258 ("Thibert"; copy attached hereto as Exhibit 2), Remington, and Makooi:

10.A. Thibert describes superdisintegrant hydration studies using an environmental scanning electron microscope (ESEM). Thibert refers to croscarmellose sodium, sodium starch

glycolate, and crospovidone as superdisintegrants. The hydration behavior of these substances was observed in the ESEM as the relative water vapor pressure was gradually increased from a level corresponding to 40% relative humidity (RH) at 15°C to a level corresponding to 80% RH at 15°C. Particles of croscarmellose sodium were observed to undergo considerable twisting and expansion at 80% RH. Sodium starch glycolate particles were observed to undergo swelling, deformation and fusion at 80% RH. Crospovidone particles, on the other hand, did not exhibit swelling at 80% RH. Sodium chloride and microcrystalline cellulose were employed as reference materials in the study. No changes in morphology and no swelling were observed for particles of microcrystalline cellulose after prolonged exposure to 80% RH which, Thibert comments (2nd column, p. 1256), is "consistent with the limited disintegrant properties of this material". Thibert concludes in part (2nd column, p. 1256) that the ESEM technique "provided direct visual confirmation of the importance of swelling as a mechanism of action for two commercially available superdisintegrants, croscarmellose sodium and sodium starch glycolate." Thibert also speculates that the superdisintegrant crospovidone operates by a mechanism other than swelling, such as wicking.

10.B. Remington provides further evidence that the art recognizes certain substances to belong to a special class of disintegrants known as superdisintegrants. The section entitled "Disintegrants" on p. 1619 of Remington defines the term disintegrant and discloses that materials serving as disintegrants include "starches, clays, celluloses, algins, gums and cross-linked polymers." This section of Remington later discloses "a group of materials known as *super disintegrants* have gained in popularity as disintegrating agents", notes that these materials are so named because they are typically completely effective at low levels, and identifies croscarmellose, crospovidone, and sodium starch glycolate as superdisintegrants. Remington then describes mechanisms by which these materials are postulated to work: Consistent with the observations in Thibert, Remington notes that sodium starch glycolate and croscarmellose swell several fold in short times, whereas crospovidone does not, and then indicates that crospovidone must operate by a mode of action other than swelling, such as wicking or capillary action.

10.C. Makooi recognizes that there is a special class of disintegrants called superdisintegrants. Similar to Remington, the reference discloses that starches, clays, celluloses, algins, gums and cross-linked polymers can serve as disintegrants, that there is a group of disintegrants called superdisintegrants, and that croscarmellose, crospovidone, and sodium starch glycolate are examples of superdisintegrants (see col. 1, lines 52-59). Makooi further discloses that its invention employs a very high level of a superdisintegrant (col. 2, lines 20-25).

11. The person of ordinary skill in the art would clearly interpret the results presented in Thibert and the description of disintegrants presented in Remington and Makooi as strong support for the proposition that a special class of disintegrants called superdisintegrants exists wherein each member of the class is characterized by being a much more effective disintegrant than other materials having disintegrant properties. The person of ordinary skill would further conclude that croscarmellose, crospovidone, and sodium starch glycolate are superdisintegrants. Particularly in view of Thibert, the person of ordinary skill in the art would understand that croscarmellose sodium and sodium starch glycolate are superdisintegrants and that microcrystalline cellulose is not, based upon their respective swelling behaviors.

12. It is accordingly my opinion that the art recognizes superdisintegrants as a special class of disintegrants; i.e., the terms are distinct and not interchangeable. In particular, croscarmellose (e.g., croscarmellose sodium), sodium starch glycolate, and crospovidone are superdisintegrants. Even more particularly, croscarmellose sodium is a superdisintegrant and microcrystalline cellulose is not.

15. I hereby declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

10th August 2005
Date

Conrad S. Winters

EXHIBIT I
DECLARATION OF CONRAD S. WINTERS
US SERIAL NO. 09/894,921 (20243CA)

I. PERSONAL

A. Name: Conrad S. Winters

B. Residence: Lansdale, PA 19446

II. EDUCATION

School	Date	Major	Degree
Bradford University, Bradford, UK	1993	Pharmaceutical Technology	Ph.D.
Bradford University	1989	Pharmacy	B.Pharm.

III. MERCK/MSDRL EMPLOYMENT HISTORY

Title	From-To
Visiting Scientist/Postdoctoral Fellow	May 1993- March 1995
Senior Research Pharmacist	March 1995- February 1998
Research Fellow	February 1998 – March 2001
Director PR&D Merck Frosst	March 2001 – December 2002
Director PR&D Pharm Physics (WP)	January 2003- October 2003
Director Formulation Development (WP)	October 2003 - Present

IV. NON-MERCK EMPLOYMENT HISTORY

Medimart Chemists , Part time Locum Pharmacist	1990 to 1993
Torbay Hospital, Torquay, Devon, UK Basic grade Pharmacist	June 1989 to Sept. 1989
Torbay Hospital, Torquay, Devon, UK Pre-registration Pharmacist	Sept 1988 to March 1989
Cyanamid UK, Fareham, Hants, UK Pre-registration student	March 1987 to Sept 1987

V. ACADEMIC EXPERIENCE

Title	From - To
John Abbott College Pharm. Tech Course Instructor	1996-1999
Bradford University, Lab Instructor Department of Pharmacognosy Department of Industrial Pharmacy	1989-1992

VI. TRAINING

Course/Conference	Subject	Date
Sloan Management School	Managing Technical Professionals and organizations	2004
Merck	Love 'Em or Lose 'Em	2004
Merck	Situational leadership	2004
Merck	Financial Management training	2004
Stat-Ease	Statistics for Scientists	2003
McGill International Executive Institute	Essential Management Skills	2002
Merck	Internal development team (IDT) training	2002
Development Dimensions Intl		
Targeted Selection	Interview techniques	2001
AIChE	Advanced Pilot plant design	2001
Merck	Facilitative leadership training II	1999
Merck	Facilitative leadership training I	1998
AIChE	Flow of Solids	1997
Merck	Effective Listening	1997
AAPS, Arden House	Pharmaceutical Powders- Properties, Processing & Regulatory Issues	1997
Thomas Engineering	New Technologies	1996
Merck	People Skills in Managers	1996
MIT	Advances in Controlled Release Techn.	1995
Merck	GMP Training	1994
Merck	Thinking for a Change	1994
Dow Chemical	Controlled Release	1993
Warner Jenkinson	Aqueous Coating	1993
Royal Soc. of Chemistry	Polymorphs & Solvates of Drugs	1992

VII. SOCIETY MEMBERSHIPS

American Association of Pharmaceutical Scientists
Institute of Chemical Engineers Particle Technology Group
Royal Pharmaceutical Society of Great Britain

VIII. ACADEMIC AND PROFESSIONAL HONORS

Bristol-Myers Squibb/SERC case award 1989-1993

IX. PUBLICATIONS AND PATENTS

Published papers and abstracts

Effect of cyclodextrin complexation on the rate of hydrolysis of gliclazide. **C. Winters**, P. York, P. Timmins and A.M. Dyas, J. Pharm. Pharmacol. 43(S) 6P, 1991.

The formation of solid state inclusion complexes of gliclazide with a range of cyclodextrins. **C. Winters**, P.York and P. Timmins, Pharm. Res. 8, S104, 1991.

Characterisation of a solid state complex of gliclazide with beta-cyclodextrin. **C. Winters**, P. York and P. Timmins, Pharm. Res. 8, S104, 1991.

Characterisation of a □-cyclodextrin:gliclazide complex using N15 solid state nuclear magnetic resonance(SSNMR). **C. Winters**, P. York, P. Timmins, R. Yeung and D. Apperly, J. Pharm. Pharmacol. 44(S) 1062, 1992.

Physicochemical characterisation and modelling of a beta-cyclodextrin gliclazide inclusion complex, **C. Winters**, P. York and P. Timmins, Proc. Sixth Int. Cyclodextrin Symp., April, 1992.

Improved Bioperformance of gliclazide on complexation with Beta-cyclodextrin. C. Winters, H.Chrystyn, P. York, P. Timmins, P. Bramley and R. Burgal, Pharm. Res., 10, S263, 1993.

Solid state characterisation of gliclazide, **C. Winters**, P. York, and P. Timmins J. Pharm. Sci. 83, 300-303, 1994.

Solid state examination of a gliclazide beta-cyclodextrin complex, **C. Winters**, P. York, and P. Timmins European Journal of Pharmaceutical Sciences, Vol 5, pp 209-214, 1997

Indomethacin Topical Polymer Film:Non Correlation of *In Vitro* and *In Vivo* Studies. **C. Winters**, S.-D. Clas, E. Kwong, D. Meisner and E. B. Vadas.Proc. Int. Symp. Control. Rel. Bioact. Mat. 22, 360-361, 1995.

An Investigation of Cyclodextrin-Drug Complexes: True Complexes or Electrostatic Adducts? H. Gagnon, J. Visentini and **C. Winters** Proceedings of the 44th Annual Meeting of the American Society for Mass Spectrometry and Allied Topics, Portland, OR, 1996.

Antiinflammatory efficacy of a novel topical indomethacin delivery system using a carrageenan-induced edema model in the fuzzy rat. E. Kwong, **C. Winters**, D. Meisner, E. B. Vadas, C.-C. Chan, R. Gordon and C. Townsley Pharm Res. Vol 13 S-367 1996.

A Feasibility Study of Cyclodextrin Inclusion Complex Quantification by IonSpray Mass Spectrometry , H. Gagnon, J. Visentini and **C. Winters** - Proceedings of the 45th Annual Meeting of the American Society for Mass Spectrometry and Allied Topics, Palm Springs, May, 1997

Pharmaceutical Applications of IonSpray LC/MS for Cyclodextrin Analysis
Josie Visentini, Angelo Filosa, Caroline Rousseau and Conrad Winters
Proceedings of the 43rd ASMS Conference on Mass Spectrometry and Allied Topics
(Atlanta, Georgia) May 21-26, 1995 p. 178.

An Investigation of Cyclodextrin-Drug Complexes:True Complexes or Electrostatic Adducts?
J. Visentini, M.J. Bertrand, H. Gagnon, C. Rousseau and C. Winters
Proceedings of the 44th ASMS Conference on Mass Spectrometry and Allied Topics
(Portland, Oregon) May 12-17, 1996. p. 1368

Effect of Particle Size Distribution on Local Voidage in a Conical Fluidized Bed H. Tanfara, T. Pugsley and **C. Winters** Presented 50th Canadian Chemical Engineering Conference, Montreal, PQ, Canada, October, 2000

Evaluation of Fluid Bed Dryer Process Parameters on the Final Particle Size Distribution of a Wet Granulation, **C. Winters**, H. Tanfara and T. Pugsley. AAPS Pharm Sci, 2000

Radial Voidage Profiles in a Fluidized Bed of Conical Cross-Section H. Tanfara, T. Pugsley and **C. Winters** Proceedings from Fluidization X, Beijing, China, May 20-25, 2001

Visualization of water content, and water distribution, within intact pharmaceutical tablets through magnetic resonance imaging, W. van der Zwaag, P. Szomolanyi, H. Tanfara, **C. Winters**, B. Balcom, 2004 submitted to J. Controlled Release.

G. Chaplin, T. Pugsley, and **C. Winters**, 2004. Application of Chaos Analysis to Fluidized Bed Drying of Pharmaceutical Granulate. Fluidization XI: Present and Future for Fluidization Engineering, U. Arena, R.Chirone, M. Miccio and P. Salatino, eds., Engineering Foundation, 419-426.

Optimization of a high shear wet granulation process using Quantisweb and JMP, H. Tanfara, F. Tavanayanfar, D. Meisner, **C. Winters**, Y. Brousseau, G. Emond, M. Mountassir, 2004 AAPS, Baltimore

Application of chaos analysis to pressure fluctuation data from a fluidized bed dryer containing pharmaceutical granule T. Pugsley, G. Chaplin and **C. Winters**, Powder Tech, Vol 142, 2-3, pg 110-120 , 2004.

The *S*-statistic as an early warning of entrainment in a fluidized bed dryer containing pharmaceutical granule T. Pugsley, G. Chaplin and **C. Winters**, Powder Tech.., Vol 149, 2-3, pg 148-156, 2005

Patents

WO95/30409 Topical Polymeric Drug Delivery System **C. Winters**, S.-D. Clas, E. Kwong, D. Meisner, E.B. Vadas

US 6,063,811 Issued May 16, 2000 Composition for once a day treatment of cyclooxygenase mediated diseases. B. Hancock, **C. Winters**, B. Gertz and E. Ehrich

Oral Presentations

Effect of cyclodextrin complexation on the rate of hydrolysis of gliclazide presented at the British Pharmaceutical Conference, Liverpool, Sept, 1991.

Characterisation of a beta-cyclodextrin:gliclazide complex using N15 solid state nuclear magnetic resonance(SSNMR), presented at the British Pharmaceutical Conference, Liverpool, Sept, 1992.

In Situ Monitoring of Drying in a Fluid Bed Drier by NIR Analysis - presented at the 1997 Canadian Pharmaceutical NIR Users Meeting, September, 1997

From molecule to medicine – the development of a drug, Key note speaker West Virginia undergraduate research symposium October, 1999